Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study

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Objective: To investigate the clinical improvement observed in patients with advanced cancer and hypoactive delirium after the administration of methylphenidate hydrochloride. **Methods:** Fourteen patients with advanced cancer and hypoactive delirium were seen between March 1999 and August 2000 at the Palliative Care Day Hospital and the inpatient Tertiary Palliative Care Unit of Montreal General Hospital, Montréal. They were chosen for inclusion in a prospective clinical study on the basis of (1) cognitive failure documented by the Mini-Mental State Examination (MMSE), (2) sleep–wake pattern disturbances, (3) psychomotor retardation, (4) absence of delusions or hallucinations, and (5) absence of an underlying cause to explain the delirium. All patients were treated with methylphenidate, and changes in their cognitive function were measured using the MMSE. **Results:** All 14 patients showed improvement in their cognitive function as documented by the MMSE. The median pretreatment MMSE score (maximum score 30) was 21 (mean 20.9, standard deviation [SD] 4.9), which improved to a median of 27 (mean 24.9, SD 4.7) after the first dose of methylphenidate ($p < 0.001$, matched, paired Wilcoxon signed rank test). One patient died before reaching a stable dose of methylphenidate. In the other 13 patients, the median MMSE score further improved to 28 (mean 27.8, SD 2.4) ($p = 0.02$ compared with the median MMSE score documented 1 hour after the first dose of methylphenidate). All patients showed an improvement in psychomotor activities. **Conclusions:** Hypoactive delirium that cannot be explained by an underlying cause (metabolic or drug-induced) in patients with advanced cancer appears to be a specific syndrome that could be improved by the administration of methylphenidate.

Objectif : Étudier l'amélioration clinique observée après l'administration de chlorhydrate de méthylphénidate (méthylphénidate) chez des patients atteints de cancer au stade avancé et présentant un délire hypoactif. **Méthodes :** Entre mars 1999 et août 2000, à un hôpital de jour en soins palliatifs et l'unit d'hospitalisation en soins palliatifs, Montreal General Hospital, Montréal, on a examiné 14 patients atteints de cancer au stade avancé et présentant un délire hypoactif. On a choisi ces patients pour les inclure dans une étude clinique prospective en fonction (1) de la défaillance de la cognition documentée par le mini-examen de l'état mental (MEEM), (2) des troubles du cycle veille-sommeil, (3) du retard psychomoteur, (4) de l'absence d'illusions ou d'hallucinations et (5) de l'absence de cause sous-jacente pour expliquer le délire. Tous les patients ont été traités au méthylphénidate, et l'on a mesuré les changements de leur fonction cognitive au moyen du MEEM. **Résultats :** Les 14 patients ont montré une amélioration de la fonction cognitive documentée par le MEEM. Le résultat médian de l'administration du MEEM avant le traitement (résultat maximal de 30) s'est établi à 21 (moyenne de 20,9, écart type [ET] de 4,9), et s'est amélioré pour atteindre une médiane de 27 (moyenne de 24,9, ET de 4,7) après la première dose de méthylphénidate ($p < 0,001$, test de Wilcoxon pour observations appariées). Un patient est mort avant qu'on atteigne une dose stable de méthylphénidate. Chez les 13 autres patients, le résultat médian au MEEM s'est amélioré encore pour atteindre 28 (moyenne de 27,8,

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ET de 2,4) (p = 0,02 comparativement au résultat médian obtenu au MEEM documenté une heure après l'administration de la première dose de méthylphénidate). Tous les patients ont montré une amélioration des activités psychomotrices. **Conclusions :** Le délire hypoactif qu'il est impossible d'expliquer par une cause sous-jacente (métabolique ou d'origine médicamenteuse) chez les patients atteints de

Introduction

Most patients with advanced cancer will experience delirium before death.[1,2] Usually, multiple possible clinical factors are implicated in the genesis of the delirium.[1] In 50% of patients, interventions such as hydration, discontinuation of psychoactive drugs, and reduction of opioid dose or opioid rotation are successful in reversing the delirium.[1,2] For some patients, the presence of underlying irreversible medical conditions (e.g., renal failure, liver failure, respiratory failure) dictates the need for symptomatic treatment alone. Lawlor et al[1] found that in a population of patients with a first episode of delirium, 40% presented with a purely hypoactive subtype. Hypoactive delirium is characterized by drowsiness, decreased physical activity, sleep–wake pattern disruption and decreased cognitive function.[3] Weitzner et al[4] reported 3 cases of neurobehavioural slowing associated with cancer that were improved with the administration of methylphenidate hydrochloride. Morita et al[5] reported their successful experience with the use of methylphenidate in 1 patient with hypoactive delirium. Other authors have suggested a potential benefit to patients with opioid-induced drowsiness.[6,7] We hypothesized that methylphenidate could improve cognitive function and other symptoms associated with hypoactive delirium in patients with cancer. We report the results of our clinical experience regarding the use of methylphenidate in the treatment of patients with hypoactive delirium in the absence of identifiable underlying causes.

Methods

Patients seen between March 1999 and August 2000 at the Palliative Care Day Hospital (allowing a minimum of 4 hours of observation) or in the inpatient Tertiary Palliative Care Unit of Montreal General Hospital, Montréal, were prospectively screened for cognitive failure using the Mini-Mental State Examination (MMSE) developed by Folstein et al.[8] Patients were considered to have cognitive failure if their MMSE score was lower than their normal expected score for age and education or if, when a previous MMSE score was present in the chart, it had decreased by at least 2 points (maximum score of 30). Patients with documented cognitive failure were fully evaluated through the taking of a complete medical history and physical examination, a review of relevant recent blood test results and radiologic imaging. When the patient, if competent, or the family agreed, further investigations were performed to rule out possible underlying causes. The diagnosis of delirium was based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[9] If the patient was manifesting any signs of hyperactivity during the observation period, or if the family or professional (for hospital inpatients) caregivers reported any history of agitation during the previous days, the patient was considered to have a hyperactive form or mixed form (hypoactive and hyperactive) of delirium. These patients were not considered to be eligible candidates for methylphenidate. Furthermore, any patient with hypoactive delirium and signs of opioid toxicity, severe myoclonus, hallucinations and delusions, or with reversible identifiable underlying causes for the delirium was excluded because of the increased risk of transforming the delirium from a hypoactive to a hyperactive form. The clinical and laboratory parameters used to define the potential causes of delirium were those described by Lawlor et al.[1] In brief, any metabolic causes were excluded, all unnecessary psychoactive drugs were discontinued, opioid dose was decreased if possible or a switch in the type of opioid was performed, and delirium was

Box 1: Clinical characteristics of hypoactive delirium without a clinically identifiable cause

- Syndrome meets DSM-IV criteria for delirium
- Clinical syndrome presents as an acute change over a few days to a few weeks
- Prodrome characterized by insomnia and daytime drowsiness
- Cognitive deficits:
  - Preservation of orientation regarding time, space and person, except in severe impairment
  - Attention deficits: decreased ability to read, watch television, make telephone calls and so on
  - Short-term memory is affected early on
  - Disorganized thinking and speech, leading to an inability to communicate with family members or friends
  - Documented cognitive failure on formal testing
- Psychomotor retardation with sensation of extreme fatigue
- Flat affect to sadness
- Neurologic abnormalities
  - From slurred speech to frank dysarthria
  - From micrographia to dysgraphia
  - From decreased muscular tone to completely bedbound
- Absence of delusions, misperceptions and hallucinations
- Absence of agitation
- Absence of metabolic, infectious, hematologic, cardiopulmonary or other disorders explaining the delirium
- Medication unlikely to be the cause of delirium

Note: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.[9]

monitored for reversal for at least 1 week.

If the delirium persisted despite aggressive efforts to reverse correctable causes, and the patient had the clinical features outlined in Box 1, the diagnosis of hypoactive delirium was reached. We then explained to the patient (when we were able to communicate with them) and family caregivers the clinical situation and offered them the opportunity of a trial of methylphenidate, explaining the potential benefits and risks, especially of hallucinations and agitation. After verbal consent was obtained, all patients were administered a 10-mg test dose of methylphenidate orally. Patients were under constant nursing supervision, including hourly monitoring of vital signs for 2 hours. The MMSE was repeated 1 hour after methylphenidate administration, using different words for recall and spelling to prevent a learning effect. When there were no distressing side effects, patients were administered the following regimen of methylphenidate, 10 mg orally twice a day (8 am and noon). Follow-up was daily for hospital inpatients and every 3–4 days for patients in the community. The MMSE was repeated at each follow-up visit. Doses of methylphenidate were increased in 5-mg increments to reach resolution of delirium, to maximum tolerable dose or to the patient's satisfaction. Follow-up continued until recurrence of delirium or death.

Descriptive statistics are used to present the results, and the significance of changes in MMSE scores was tested using a matched, paired Wilcoxon signed rank test (2-tailed distribution). Significance was set at $p \leq 0.05$.

Results

The clinical characteristics of the 14 patients who were enrolled in the study are listed in Table 1. All patients had advanced metastatic cancer and were not candidates for further chemotherapy. Four patients had brain metastases that had been previously treated with radiotherapy. Eight patients were not taking any strong opioids, whereas 3 other patients were taking less than 100 mg of a morphine equivalent per day. Table 1 also provides a complete list of all the drugs with potential effects on the central nervous system that the patients were taking. These drugs were mainly taken for symptom management, and their initiation of administration did not correspond with the onset of the delirium.

The effect of methylphenidate on the MMSE scores over time is shown in Table 2. The median pretreatment MMSE score (maximum score 30) was 21 (mean 20.9, standard deviation [SD] 4.9), which improved to a median of 27 (mean 24.9, SD 4.7) after the first dose of methylphenidate ($p < 0.001$, matched, paired Wilcoxon signed rank test). One patient died before reaching a stable dose of methylphenidate. In the other 13 patients, the median MMSE score further improved to 28 (mean 27.8, SD 2.4) ($p = 0.02$ compared with the median MMSE score documented 1 hour after the first

Table 2: Changes in Mini-Mental State Examination (MMSE) scores of patients with hypoactive delirium from previous MMSE (T_{-1}) to the time of diagnosis (T_0), 1 hour after the first dose (T_1) and at a stable dose of methylphenidate (T_2)

		MMSE score		
Time	No. of patients	Median	Mean	Standard deviation
T_{-1}	10	28	28.5	0.9
T_0	14	21*	20.9	4.9
T_1	14	27†	24.9	4.7
T_2	13	28‡	27.8	2.4

Note: Significance was calculated using a matched, paired Wilcoxon signed rank test (2-tail distribution).
*Comparing T_0 with T_{-1}, $p = 0.005$.
†Comparing T_1 with T_0, $p < 0.001$.
‡Comparing T_2 with T_1, $p = 0.02$.

Table 1: Patients' characteristics at diagnosis of hypoactive delirium

Patient no.	Sex	Age, yr	Cancer type	Brain metastases*	Type of opioid	Daily dose of opioid, mg	Other psychoactive drugs (and oral daily dose)
1	M	46	Lung	Yes	Morphine	30	Phenytoin (500 mg), famotidine (40 mg), dexamethasone (12 mg)
2	M	51	Lung	Yes	—	—	Dexamethasone (4 mg)
3	F	62	Colon	—	Codeine	300	Prednisone (5 mg)
4	M	80	Testicular	—	—	—	—
5	M	65	Lung	Yes	Morphine	90	Celecoxib (200 mg), phenytoin (300 mg), omeprazole (20 mg), dexamethasone (8 mg), metoclopramide (10 mg)
6	F	44	Rectal	—	Morphine	90	Sertaline (50 mg), omeprazole (20 mg), prednisone (25 mg)
7	M	65	Lung	—	Morphine	280	—
8	M	80	Lung	—	—	—	Methotrimeprazine (5 mg), dexamethasone (4 mg)
9	M	64	Prostate	—	Methadone	75	Methotrimeprazine (10 mg), dexamethasone (16 mg), metoclopramide (40 mg)
10	M	66	Lung	—	—	—	Methotrimeprazine (5 mg), metoclopramide (30 mg)
11	F	61	Lung	—	—	—	—
12	F	41	Cervix	—	Morphine	120	Metoclopramide (60 mg)
13	F	79	Breast	Yes	—	—	Dexamethasone (16 mg)
14	M	57	Prostate	—	—	—	Methotrimeprazine (25 mg), dexamethasone (2 mg)

*All patients with brain metastases received radiotherapy (10 Gy).

dose of methylphenidate). All patients had a positive response to methylphenidate that included increased alertness, partial-to-complete resolution of psychomotor retardation, and normalization of slurred speech. All patients felt a marked increase in their energy level. Of note, 10 patients had a previously documented normal MMSE score before the occurrence of the hypoactive delirium. Patient 10 did not improve cognitively but still had marked improvement in his psychomotor activity. He resumed eating by himself and making telephone calls. Figure 1 shows the changes produced by the occurrence of delirium and the administration of methylphenidate over time on the drawing and writing abilities of patient 1 and the drawing abilities of patient 3, as tested by the MMSE. The drawings and the writings are quite characteristic with loss of spatial orientation, micrographia and dysgraphia. Patients with a very severe syndrome were unable to write and draw.

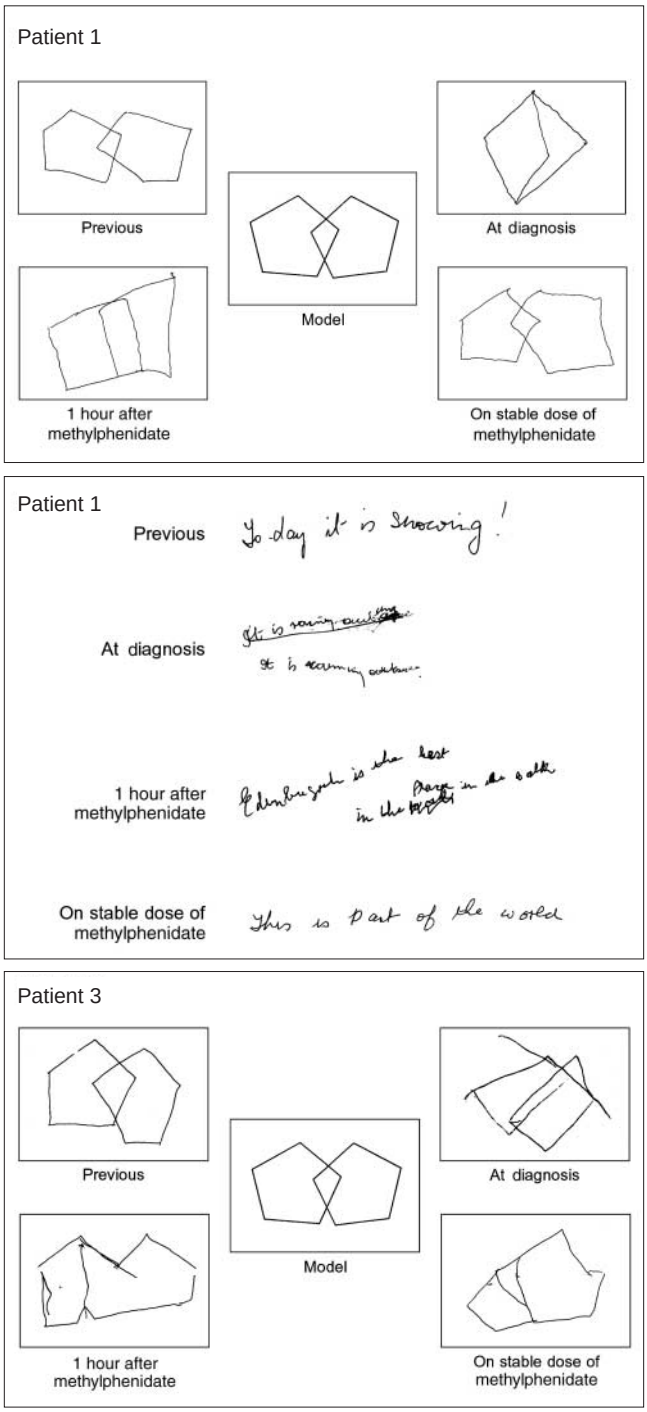

Fig. 1: Examples of changes over time induced by hypoactive delirium and treatment with methylphenidate in the drawing and writing abilities of patients with advanced cancer.

Most patients were treated adequately with a dose of 20–30 mg per day of methylphenidate; the maximum effective daily dose given was 50 mg. Higher doses were not associated with further improvements but, instead, with increased side effects, mainly nervousness, and the dose needed to be reduced to 50 mg daily. When the effective dose was reached, patients usually maintained a sustained response until a few days before death. At that point, a patient's cognitive function would start to fall again until the patient entered into a coma and died. The condition of patient 12, despite an initial response, deteriorated quickly the next day, and the patient could not be started on a regular dosage of methylphenidate.

The details of the cognitive deficits tested using the MMSE are listed in Table 3. The worsening of the cognitive impairment seemed to follow a pattern: first there were recall deficits, then attention and language deficits. The language praxic deficits were characterized by writing and drawing deficits, and only in severe cases did verbal deficits become apparent. Orientation in time and space and registration, that is, the ability to retain 3 new objects, remained quite well preserved even in severe cases. Improvement occurred first in drawing and writing, and then in attention. Recall remained partially impaired in most cases. The survival of the patients ranged from 4 days to 205 days, with a median survival of 39.5 days. The 3 patients with less than 2 weeks' survival all had severe cancer cachexia.

Discussion

We studied 14 patients with advanced cancer who were in the palliative phase of their illness. They presented with a disturbance in their mental status that could most appropriately be diagnosed as delirium–hypoactive.[10] Hypoactive delirium is not uncommon; what is remarkable is the absence of any apparent cause of the patients' state of confusion and the relative homogeneity of the clinical presentation (Box 1).

Opioids are known to produce drowsiness and decreased cognitive function in patients with cancer in the context of toxicity.[1] In most instances, the associated delirium is of the hyperactive type. Moreover, in this group of patients, 8 were not receiving strong opioids; most of the others were receiving low-dose morphine. Opioids were most probably not responsible for the hypoactive delirium identified.

The delirium may have been caused by the concurrent exposure to psychoactive drugs.[1,11,12] Most of the patients were taking at least 1 of these drug classes; however, these drugs were given in relatively low doses, and their initiation bore no

temporal relationship to the onset of the delirium. Thus, they were unlikely to have caused the changes in cognitive status.

The hypoactive quality in these patients raises the prospect of apathy syndrome.[13] The coincident cognitive and behavioural phenomena prompt the overriding diagnosis of delirium.

Similarly, the patients' profound psychomotor retardation and drowsiness may suggest a diagnosis of depression. The spontaneous denial by 6 of these patients of any subjective feelings of sadness or depression, their reversed sleep–wake cycle and the cognitive deficits in recall, attention, agraphia and figure reproductions contradict such a conclusion.[14]

In the absence of metabolic or endocrinologic explanations, or any toxic provocation, and the absence of any space-occupying lesions visualized on cranial computed tomography, and in the presence of known malignancies, we must pursue other possible causes.

In 4 patients, the hypoactive delirium could have been delayed sequelae of whole-brain radiotherapy. Another possibility would be a late consequence of chemotherapy: most of these patients had received chemotherapy but none at the time of the presentation of this cognitive dysfunction. Offsetting such an explanation is the experience that delirium induced by chemotherapy invariably occurs during the treatment and is the hyperactive type with agitation and hypervigilance.[15]

Soucy et al[16] reported that positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-D-glucose (PET-FDG) performed on a 68-year-old man who had developed hypoactive delirium subsequent to a 4-year history of metastatic adenocarcinoma of unknown origin showed diffusely decreased cortical uptake, which was worse in the temporal and posterior parietal regions. Further PET imaging done after the initiation of methylphenidate showed increased uptake in the primary motor area.

One of the criteria for a diagnosis of paraneoplasic limbic encephalitis (PLE) is the demonstration by magnetic resonance imaging of temporal lobe abnormalities.[17] PLE may have a myriad of manifestations. The triad of poor memory, confusion and mood disturbances is a frequent symptom constellation. Could this be another explanation for the hypoactive delirium? Occurring most often in patients with small-cell carcinoma,[18–21] PLE has been associated with cancer of the breast,[22] ovary,[23] prostate[24] and testicle[25] and with non-small-cell cancer of the lung.[26] It is frequently noted to present while the associated carcinoma is occult. Diagnosis may be aided by the identification of antineuronal antibodies produced in response to onconeural antigens expressed ectopically in the tumour. These antibodies are not always detected, and there are many other symptom clusters associated with PLE.[26] A quartet of criteria has been developed to authenticate this diagnosis.

The patients described here do not meet the criteria for PLE. The sequence of presentation having been reversed, no evidence of these antineuronal antibodies can be offered (serologic testing was not carried out on these patients in the terminal phase of their illness). Cerebrospinal fluid findings are also absent.

May we develop an explanation from a better understanding of the putative effects of methylphenidate? Methylphenidate, a piperidine-derived stimulant, namely, methyl-alpha-phenyl 2-piperidineacetate hydrochloride, is frequently used in the palliative context to offset drowsiness induced by high doses of opioids[6,7,27] and in the treatment of depression in medically ill patients, including those with cancer.[4,27–34] In individuals with brain injuries,[29] improvement of memory and attention, alleviation of certain neurobehavioural symptoms and successful treatment of post-traumatic narcolepsy and brain injury–related anger have all been ascribed to methylphenidate.[35–37] Management of HIV-related cognitive decline using methylphenidate has produced inconsistent results. Anecdotal reports have identified a treatment role for methylphenidate in reducing the duration of coma, particularly that induced by brain trauma.[35] In attention-deficit hyperactivity disorder (ADHD), methylphenidate has a demonstrated function both in regulating inattention and in containing behavioural disruption.[38] To the best of our knowledge, this is the first study, other than that by Morita et al[5] of 1 patient whose hypoactive delirium was related to multiorgan failure, to look prospectively at the use of methylphenidate to treat hypoactive delirium in a sample of terminally ill patients with cancer.

Table 3: Details of cognitive deficits on the MMSE of patients with hypoactive delirium at the time of diagnosis (T_0), 1 hour after the first dose (T_1) and at a stable dose of methylphenidate (T_2)

Deficit	No. of patients	Time	MMSE, range	Feature; median value				
				Orientation	Registration	Attention	Recall	Language
Severe	4	T_0	12–16	6	2	0.5	0	5
	4	T_1	15–23	7.5	3	1	0.5	7
	3	T_2	25–27	8	3	5	3	8
Moderate	4	T_0	20–21	8	3	0	1	7.5
	4	T_1	22–28	8.5	3	4	1	7.5
	4	T_2	22–30	9.5	3	5	1.5	8.5
Mild	6	T_0	24–27	10	3	3.5	1	8.5
	6	T_1	28–30	10	3	5	2	9
	6	T_2	27–30	10	3	5	2	9
Normal score	—	—	30	10	3	5	3	9

Methylphenidate is classified as a psychostimulant or an analeptic. The therapeutic effect has been ascribed to its neurostimulation of the reticular activation system.[35] Although the exact mechanism by which methylphenidate effects its behavioural modifications is not known, the prevailing focus is its influence on the catecholamine systems. With its greater affinity for the dopamine neurons, methylphenidate is thought to have 2 actions. Predominantly, it blocks the catecholamine transporter.[38–40] It also redistributes vesicular monoamine transporter–2 roles in dopamine nerve terminals.[41] Although the responsible nerve bodies for dopamine are in the mesencephalon, dopamine is an important neurotransmitter in the limbic system, both the dorsal and ventral striatum, the nucleus accumbens and the mesocortical system originating in the ventral tegmental area.[40] In the rat, methylphenidate blocks dopamine uptake in the striatum, nucleus accumbens, olfactory tubercles and prefrontal cortex. Extracellular levels of dopamine in the striatum and nucleus accumbens, in in-vivo microdialysis studies, have been noted to increase in response to methylphenidate.[35] A heuristic model of dopamine system functioning is that of tonic–phasic interaction.[38] Extrasynaptic supplies of dopamine regulate tonic activity. The tonic activity modulates the phasic. It has been noted that methylphenidate, when administered orally, mimics tonic dopamine cell firings.[42]

The pharmacologic effect of methylphenidate has been most extensively investigated in individuals with the diagnosis of ADHD. The cognitive–behavioural corrections associated with methylphenidate therapy have been ascribed to a restoration by methylphenidate of phasic firing in the mesolimbic dopamine pathways.[40,43] Single-photon emission computed tomography (SPECT) studies in children with ADHD have revealed, in addition to other pathologies, most notably in the prefrontal cortex, decreased temporal lobe perfusion, particularly on the right side.[44]

The tentative conclusions derived from inchoate PET studies in this population indicate dysfunction in the parietal and temporal lobes. Such dysfunction would explain the predominance of the short-term memory and praxic dysfunctions identified in our population. It does not, however, provide us with a ready explanation for the apparent corrective efficacy of methylphenidate.

The subiculum of the hippocampus is deemed to have an "important gating influence" in the regulation of the dopamine mesolimbic system.[37] The cortical dysfunctions, as appreciated in PET imaging, may not only be influential directly but also indirectly: the dysfunction may extend to induced disequilibrium in the phasic–tonic balance in the mesolimbic dopamine system.

Methylphenidate may, therefore, be addressing this dysfunction. Its ability to block dopamine reuptake, particularly in the extrasynaptic space, may allow for a correction of the phasic–tonic imbalance in the mesolimbic system. Limbic system interactions, particularly those predicated on the nucleus accumbens, anterior cingulate gyrus[44] and prefrontal cortex may be somewhat normalized with attendant

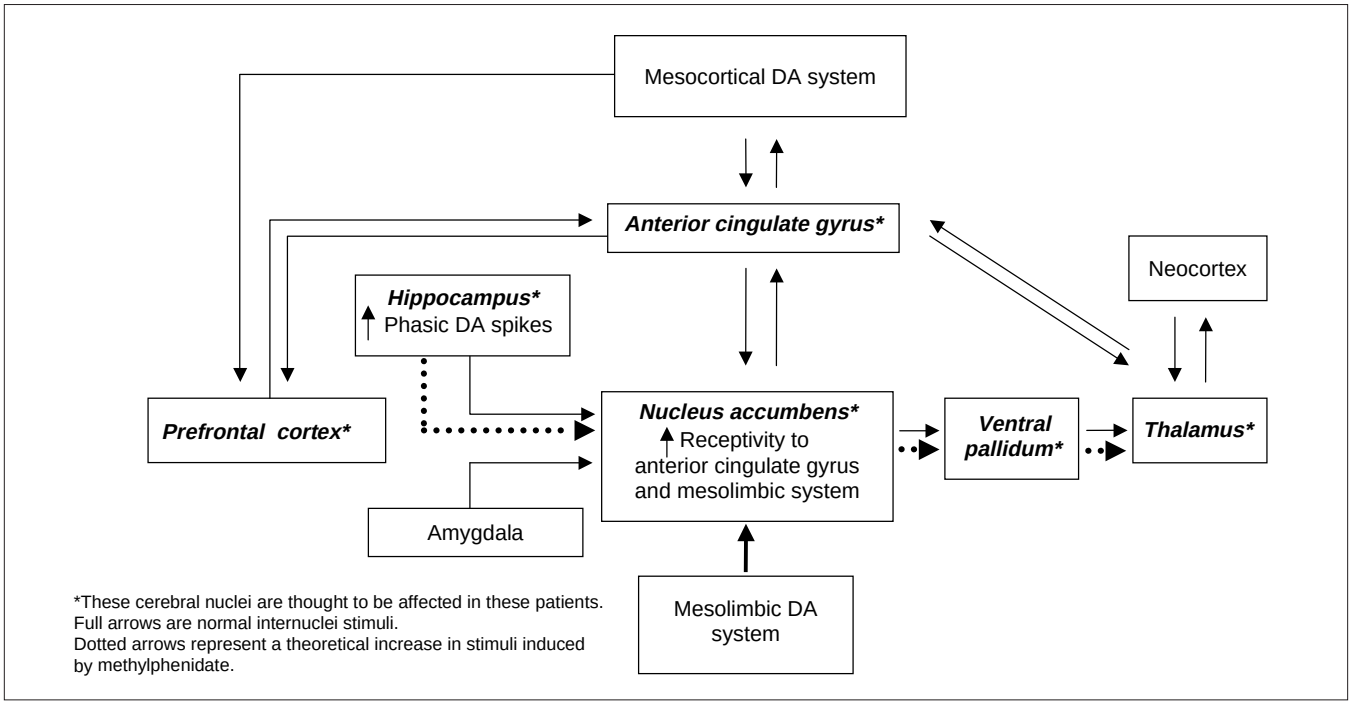

Fig. 2: Proposed modifications produced by methylphenidate in hypoactive delirium. We hypothesize that specific central nuclei [*] of the brain are affected in these patients. One consequence of this is the development of impaired phasic–tonic firing in the mesolimbic–nucleus accumbens–anterior cingulate–prefrontal circuitry. The clinical picture reflects this dysfunction. Methylphenidate, through its effect particularly on hippocampal neurons, fosters phasic dopamine (DA) spikes, promoting recovery of the phasic–tonic balance in the circuitry. It does this by its ability to block dopamine uptake, particularly in the extrasynaptic space.

restoration of memory and praxic functions (Fig. 2).

An analeptic role has historically been assigned to methylphenidate. An explanation analogous to that proposed here has been posited in the context of its therapeutic efficacy in ADHD.[29]

This clinical syndrome should be recognized in clinical practice. A trial of methylphenidate should be offered to patients who wish to improve their mental function and physical activities, once it has been explained to them that the efficacy of the drug and its potential benefits can only be conjectured, until demonstrated in randomized placebo-controlled trials. Further studies aimed at better defining the underlying pathologic processes involved in this type of delirium and its incidence and prevalence are needed to understand the importance of this syndrome and its relevance to or independence from drug interventions (namely, opioid and other psychoactive drugs commonly used in this population).

Conclusion

We studied a group of patients with advanced cancer and hypoactive delirium who experienced benefits from treatment with methylphenidate. Their clinical presentation included psychomotor retardation, cognitive failure, drowsiness and sleep–wake pattern disturbances in the absence of hallucinations and agitation. The patients' marked improvement after the administration of methylphenidate remains to be fully explained, but we have hypothesized that methylphenidate re-establishes dopamine balance, allowing proper function of the limbic system. Further studies of the phenomenology, pathophysiology and prevalence of this syndrome, and of the role of methylphenidate as a potential treatment, are essential given that delirium is a significant source of suffering for patients and families.

Competing interests: None declared.

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